New polymorphic forms of ondansetron, processes for preparing them, pharmaceutical compositions containing them and their use as antiemetics

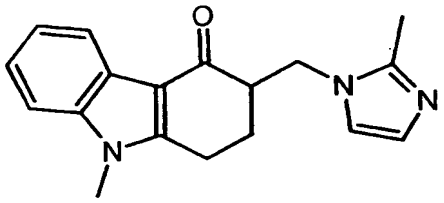
Field of the invention

This invention relates to new polymorphs of (±)1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-il)methyl]-4H-carbazol-4-one, known under the INN of ondansetron.

This invention also relates to processes for preparing said polymorphs, to pharmaceutical compositions containing them and to their use in the treatment and prophylaxis of nausea and vomiting.

Background of the invention

The compound (±)1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-il)methyl]-4H-carbazol-4-one is known under the INN of ondansetron and has the following structure:



Ondansetron is a selective antagonist of the 5-HT_3 receptor, which is marketed as an antiemetic.

Patent GB 2153821 describes ondansetron, its salts and solvates. In particular, the preparation of base ondansetron is described in several examples. Thus, in example 4, the preparation of base ondansetron is described by methylation with dimethyl sulphate in dimethylformamide; the product obtained melts with

decomposition at 223°C - 224°C. In example 7, base ondansetron is obtained by treatment of 3-[(dimethylamine)methyl]-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one hydrochloride with 2-methylimidazol in water, to yield ondansetron with a melting point of 221°C - 221.5°C, which following recrystallisation in methanol gives a melting point of 231°-232 °C. In example 8, the preparation of base ondansetron is described by treatment of 1,2,3,9-tetrahydro-9-methyl-3-methylene-4H-carbazol-4-one with 2-methylimidazol in water followed by recrystallisation in methanol, to yield ondansetron with a melting point of 232°-234 °C with decomposition. In example 18, the preparation of base ondansetron is described by reaction of 3-(chloromethyl)-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one with 2-methyl-imidazol in DMF (dimethylformamide), which following purification by column chromatography yields ondansetron with a melting point of 228°-229°C. In example 19 the preparation of base ondansetron is described by oxidation of 2,3,4,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-il)methyl]-1H-carbazol maleate with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in THF (tetrahydrofuran), which following purification by column chromatography yields ondansetron with a melting point of 227°C-228.5°C. Example 20 describes the preparation of base ondansetron by oxidation of 2,3,4,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-il)methyl]-1H-carbazol-4-ol with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in THF, which following purification by column chromatography yields ondansetron with a melting point of 227.5-229°C.

Patents GB 2220352, EP 385517 and EP 276559 also describe the preparation of ondansetron in accordance with example 7 of the above-cited patent, giving a melting point that coincides with that mentioned in said example.

Other processes have also been described for preparing ondansetron, which processes yield ondansetron with the following melting points: in patent EP 221629, following purification by column chromatography, it decomposes at 215-216°C; in patent EP 219929, following purification by column chromatography, it melts at 216-218°C and, following recrystallisation in methanol, at 227.5-228.5°C; and, finally, in patent ES 2043535, following recrystallisation in methanol, it melts at 227-228.5°C.

That is, all the references mentioned above describe ondansetron with very variable melting points that range from 215°C to 234°C. Following purification by column chromatography they remain variable, from 215°C to 229°C, and following recrystallisation in methanol the melting points rise and centre around 230°C (227-234°C).

International patent WO 03093260 discloses two crystalline forms of base ondansetron, one with a melting point similar to that described in the preceding references and another with a higher melting point, denominated, respectively, Form A and Form B. Form B has a melting point of 244±2°C and a powder X-ray diffraction pattern that is characterised by the following peaks: 11.0; 11.2; 14.9; 15.5; 15.9; 16.5; 20.6; 21.4; 23.1; 23.5; 24.2; 24.7; 24.8; 25.8; 26.9; 28.1 °2θ. Its preparation is described by dissolving base ondansetron in ethanol or methanol at reflux temperature and subsequent cooling. Form A is characterised by a powder X-ray diffraction pattern that presents the following peaks: 11.0; 11.2; 14.8; 15.4; 16.4; 20.6; 21.4; 23.2; 24.1; 24.7; 25.4; 25.9; 26.7; 27.8 °2θ. The preparation of Form A is described by recrystallisation of ondansetron in N,N-

dimethylformamide and by recrystallisation in 1-butanol.

The examples described disclose the preparation of polymorphic forms of ondansetron solely at a scale of a few grams or a maximum of 1.1 kg. Furthermore, in spite of the small amounts of product obtained, the volume of solvent that has to be used is very high (60 L of solvent are required to prepare the maximum amount described, i.e. 1.1 kg), thereby hindering its large-scale production.

It is therefore recommendable to have new stable polymorphic forms of ondansetron and processes for manufacturing them that permit the product to be produced at industrial scale.

Description of the invention

The subject-matter of the present invention is to provide three different polymorphic forms of (±)1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-il)methyl]-4H-carbazol-4-one, known under the INN of ondansetron.

Thus, a first aspect of the invention relates to a new polymorphic form of ondansetron called, hereinafter, Form C, which is characterised by presenting a powder X-ray diffraction pattern, using $K\alpha_1$ radiation of Cu, in accordance with Figure 1.

A second aspect of the invention relates to a new polymorphic form of ondansetron called, hereinafter, Form D, which is characterised by presenting a powder X-ray diffraction pattern, using $K\alpha_1$ radiation of Cu, in accordance with Figure 2.

A third aspect of the invention relates to a new

polymorphic form of ondansetron called, hereinafter, Form E, which is characterised by presenting a powder X-ray diffraction pattern, using $K\alpha_1$ radiation of Cu, in accordance with Figure 3.

Also subject-matter of the present invention are processes for preparing the new polymorphic forms of ondansetron denominated Forms C, D and E.

Another aspect of the present invention is a pharmaceutical composition that contains any of the new polymorphic forms of ondansetron, denominated Forms C, D and E.

Yet another aspect of the invention is the use of the new polymorphic forms of ondansetron denominated Forms C, D and E for manufacturing a drug for the treatment and prophylaxis of nausea and vomiting.

And an additional aspect of the invention is a therapeutic method for the treatment and prophylaxis of post-operative nausea and vomiting and for the control of nausea and vomiting induced by radiotherapy and cytotoxic chemotherapy.

Description of the figures

Figure 1 shows the powder X-ray diffraction pattern of the Form C. The y-axis represents the intensity (in counts) and the x-axis represents the angle 2 Theta.

Figure 2 shows the powder X-ray diffraction pattern of the Form D.

Figure 3 shows the powder X-ray diffraction pattern of the Form E.

Figure 4 shows the low-frequency Raman spectrum of Forms C, D and E. The y-axis shows the Raman intensity (in A.U., arbitrary units) and the x-axis the frequency.

Detailed description of the invention

The three polymorphic forms of ondansetron, subject-matter of the present invention, are identifiable by their powder X-ray diffraction patterns.

Form C, to which the first aspect of the invention relates, is characterised by a powder X-ray diffraction pattern that presents two characteristic peaks at 14.97 and 20.86° 2θ and presents no peaks beneath 6.5° 2θ. To a lesser extent, the phase is also characterised by the peak of 25.50° 2θ. The diffraction pattern of Form C presents, in relation with that of the other two polymorphs also subject-matter of this invention, a lower number of peaks in the angle interval 5 - 30° 2θ. Table 1 shows the peaks observed in a powder X-ray diffraction pattern of Form C using the conditions for providing the diffraction pattern described below. Said Table 1, further includes the relative intensity values of said peaks as additional information.

Table 1

2θ (°)	I/I_0
7.18	96
10.96	100
13.13	34
14.97	36
16.08	39
16.42	34
19.73	19
20.86	41
21.82	20
24.08	70
24.70	47
25.50	52
26.73	30
27.59	20
28.97	22

Form C presents a powder X-ray diffraction pattern, using the $K\alpha_1$ radiation of Cu, in accordance with Figure 1.

Form D, to which the second aspect of the invention relates, is characterised by a powder X-ray diffraction pattern that presents peaks at 11.29°; 14.58°; 17.16°; 18.89°; 20.28°; 21.22°; 25.06° and 27.49° 2θ. Table 2 shows the peaks observed in a powder X-ray diffraction pattern of Form D. Said Table 2 further includes the relative intensity values of said peaks as additional information.

Table 2

2θ(°)	I/I_0
5.58	16
7.10	99
7.26	49
10.77	58
10.92	86
11.29	60
13.23	50
13.65	15
14.58	43
14.74	24
15.23	21
15.38	23
15.92	30
16.22	37
16.48	42
17.16	18
17.86	15
18.89	18
20.28	39
20.71	32
21.22	40
21.98	24
22.84	16
23.53	17
24.12	74
24.75	68
25.06	100
26.03	40
26.17	39
26.56	31
26.79	24
27.49	25
27.91	21
28.75	20
29.41	18

Form D presents a powder X-ray diffraction pattern, using the $K\alpha_1$ radiation of Cu, in accordance with Figure 2.

Form E, to which the third aspect of the invention

relates, is characterised by a powder X-ray diffraction that presents peaks at 6.29°; 11.09°; 11.88°; 12.69°; 14.97° (this last peak being also present in the diffraction pattern of Form C) and a doublet (24.96°; 25.17°) 2θ. Table 3 below shows the peaks observed in a powder X-ray diffraction pattern of Form E. Table 3 further shows, as additional information, the relative intensity of said peaks.

Table 3

2θ(°)	**I/I_0**
6.29	17
7.06	67
10.50	16
11.09	100
11.88	13
12.69	16
13.10	32
13.57	16
14.97	48
16.33	53
16.93	17
17.40	15
18.58	13
19.28	19
20.71	38
21.08	23
21.28	30
22.10	20
24.12	48
24.71	41
24.96	60
25.17	87
25.73	24
26.65	34
26.93	21
28.18	19
28.53	17
29.34	15
29.76	15

Form E presents a powder X-ray diffraction pattern, using the $K\alpha_1$ radiation of Cu, in accordance with Figure 3.

Advantageously, Form E can also be prepared in a manner reproducible at industrial scale, which makes it the optimum crystalline form of ondansetron for marketing and, therefore, the preferred form.

The powder X-ray diffraction patterns were obtained with $K\alpha_1$ radiation of Cu, using an INEL CPS-120 appliance with Ge primary monochromator and in transmission geometry with the samples inside 0.5 mm diameter Lindemann glass capillary tubes. The error in determination of the position of the peaks can be estimated at ±0.05 °2θ.

Differences were also discerned between the three polymorphic forms C, D and E in the low-frequency region (between 15 and 150 cm^{-1}) of the Raman spectra, as shown in Figure 4. The Raman spectra of Forms C and D are more similar to each other, while they show a clear spectral difference in relation to Form E. The Raman technique is therefore not very suitable for distinguishing Forms C and D from one other, although it does permit these two forms to be distinguished from Form E.

The Raman spectra were obtained using Jobin-Yvon T64000 equipment with an argon laser, and the determination was carried out using an excitation wave of 514.5 nm and laser power between 30 and 35 mW.

The three polymorphic forms of the present invention present melting points in a range of 240-247 °C. The melting points were determined by DSC, on the basis of

the melting peak, using an aluminium crucible with perforated lid at a heating rate of 10 °C/min. Taking into account that the melting temperatures of the three polymorphs of the invention are similar, and given that base ondansetron melts with decomposition to release 2-methylimidazol, melting temperature is not considered to be a characteristic that permits the three forms of the invention to be distinguished from one another.

There follows a detailed description of the processes for preparing the three polymorphs denominated Forms C, D and E of the invention.

Thus, Form C can be obtained by addition of a precipitating solvent to a saturated solution of base ondansetron at room temperature. More specifically, Form C can be prepared by means of a process that comprises:

a) preparation of a saturated solution of base ondansetron at room temperature in dichloromethane;
b) precipitation of the crystalline form by addition of a C_5-C_7 alkane; and
c) recovery of the crystalline form.

Preferably, said C_5-C_7 alkane is chosen from n-hexane or n-pentane.

Form D can be prepared by a process that comprises:

a) dissolution of base ondansetron in a C_1-C_4 alcohol at reflux;
b) addition of *t*-butyl-methyl-ether followed by cooling; and
c) recovery of the crystalline form.

Preferably, said C_1-C_4 alcohol is methanol.

This invention also provides a process for manufacturing Form E. Said process comprises:

a) dissolution of the ondansetron hydrochloride in a mixture of a C_1-C_3 alcohol and water;
b) precipitation of the base ondansetron by basification of the solution;
c) filtering the solid and washing with water;
d) suspension of the water-moistened solid obtained in stage c) with methanol at reflux with stirring; and
e) recovery of the crystalline form.

Preferably, said C_1-C_3 alcohol is methanol.

The basification of stage b) can be carried out by means of addition of a solution of sodium hydroxide, potassium hydroxide or aqueous ammonia. Preferably, the basification of stage b) is carried out by addition of an aqueous ammonia solution. Advantageously, the basification with aqueous ammonia produces ammonium chloride as a residue, which is much more soluble in water and in alcohols than sodium or potassium chloride and therefore much easier to eliminate.

Advantageously, said process permits Form E to be obtained in a manner perfectly reproducible at industrial scale. Moreover, as it does not require complete dissolution of the base ondansetron in an alcohol, a solvent in which it is not very soluble, it permits greater amounts of product to be obtained with very much lower volumes of solvent in comparison with the prior art.

Form E can also be prepared at laboratory scale by means of a process that comprises:

a) dissolution of the base ondansetron in a C_1-C_4 alcohol at reflux;
b) addition of ethyl acetate followed cooling and concentration by slow evaporation at room temperature and
c) recovery of the crystalline form.

Preferably, said C_1-C_4 alcohol is methanol.

Recovery of any of the polymorphic forms of the present invention is carried out by filtering the solid and drying, using conventional methods.

In this invention, "a C_1-C_4 alcohol" is taken to mean methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol.

In this invention, "a C_5-C_7 alkane" is taken to mean n-pentane, n-hexane, n-heptane.

The base ondansetron and the ondansetron hydrochloride used as starting product to prepare the polymorphic forms of the present invention can be prepared by any of the processes described in the literature. Preferably, they are obtained in accordance with the general process described in patent ES 2043535, whose industrial application is carried out with hydrochloric acid as acid catalyst, in a mixture of isopropyl alcohol and water as solvent, which permits the ondansetron to be isolated directly in the form of hydrochloride. The base ondansetron can in turn be obtained by basifying a solution of said hydrochloride.

Also subject-matter of the present invention is a pharmaceutical composition that contains any of the new

polymorphic forms of ondansetron denominated Forms C, D or E in a therapeutically active amount and with a suitable amount of at least one excipient.

The compositions provided by the present invention can be administered by any suitable route, but preferably orally or parenterally.

The compositions for parenteral or topical administration can be presented in the form of injectable solutions, intravenous solutions, infusions, suppositories or transdermal systems. The pharmaceutical compositions for oral administration can be solids such as tablets or capsules prepared by the conventional means with pharmaceutically acceptable excipients, or liquids such as aqueous or oleous solutions, syrups, elixirs, emulsions or suspensions prepared by the conventional means with pharmaceutically acceptable additives.

Tablets and injectable or intravenous solutions are preferred forms of oral and parental administration, respectively.

An especially preferred pharmaceutical form for administration of Forms C, D and E of ondansetron are orally disintegrating tablets (also called buccodispersable). Buccodispersable tablets are taken to mean uncoated tablets for placing in the mouth and having the advantage that they disintegrate rapidly before being swallowed. Various types of technologies have been described for making tablets of this type, and they are known to experts in the subject. Especially preferred are those disclosed in international patent application WO 03103629.

Said pharmaceutical forms can contain a dose of any of the Forms C, D and E, preferably a dose of 2-10 mg.

In accordance with conventional pharmaceutical practice, the excipients for the tablet forms can include diluents, disintegrants, wetting agents, lubricants, colorants, flavourings or other conventional adjuvants. Thus, typical tablet excipients include, for example, lactose, microcrystalline cellulose, corn starch, hypromellose, magnesium stearate, macrogol, polyvinylpyrrolidone, manitol.

The injectable formulations in accordance with the invention include, preferably, aqueous solutions, with conventional excipients for injectable formulations including sodium citrate, citric acid, sodium chloride, together with water for injections.

Also subject-matter of the invention is the use of any of Forms C, D and E for manufacturing a drug for the treatment and prophylaxis of post-operative nausea and vomiting and for the control of nausea and vomiting induced by radiotherapy and cytotoxic chemotherapy.

Also subject-matter of the present invention is a therapeutic method for the treatment and prophylaxis of post-operative nausea and vomiting and for the control of nausea and vomiting induced by radiotherapy and cytotoxic chemotherapy, which consists in administering to a patient who so requires a therapeutically effective amount of any of the Forms C, D or E, preferably in a dose of between 2-10 mg.

Experimental Part

There follow by way of non-restrictive illustration of the invention the following examples.

EXAMPLES OF SYNTHESIS

Example 1

Preparation of Base ondansetron Form C

492 mg of base ondansetron are dissolved in 35 mL of dichloromethane. 18 mL of n-hexane are added and crystals are seen to precipitate. The resulting suspension is stirred for 10 minutes and filtered. The white solid obtained is dried at 40°C to constant weight. 137 mg de base ondansetron Form C (28%) is obtained.

Example 2

Preparation of Base ondansetron Form C

146 mL of n-pentane is added to a stirred solution of 4 g of base ondansetron in 284 mL of dichloromethane at 20-22°C, and crystals are seen to precipitate. The resulting solution is stirred for 10 minutes and filtered. The white solid obtained is dried at 40°C to constant weight. 2 g of base ondansetron Form C (50%) is obtained.

Example 3

Preparation of Base ondansetron Form D

A stirred solution of 4 g of base ondansetron in 178 mL of methanol is heated at reflux to total dissolution. 509 mL of t-butyl-methyl-ether is added slowly and the heating then switched off and the mixture left to cool slowly with stirring down to 20-22 °C. The resulting suspension is

filtered and the white solid obtained is dried at 40°C to constant weight. 2.4 g of base ondansetron Form D (60%) is obtained.

Example 4

Preparation of Base ondansetron Form E (laboratory method)

A stirred solution of 4 g of base ondansetron in 200 mL of methanol is heated at reflux to total dissolution. 480 mL of ethyl acetate is added slowly and the heating then switched off and the mixture left to cool slowly down to 20-22 °C. The stirring is stopped and the mixture is left to concentrate slowly with the flask open for 20-30 days until crystals appear, which are filtered and dried at 40°C. 1 g of ondansetron Form E (25%) is obtained.

Example 5

Preparation of Base ondansetron Form E (industrial plant method)

A stirred suspension of 16 kg of ondansetron hydrochloride in 80 L of methanol and 80 L of water is heated at 30 °C to total dissolution. 6 L of 25% aqueous ammonia is added over the course of 2 hours, until pH 9 is reached. Base ondansetron precipitates out and the resulting suspension is heated to 35 °C and stirred at that temperature for 1 hour. It is then cooled to 22-25 °C and the suspension is centrifuged. The resulting cake is washed with water (2 x 40 L) and suspended again in 60 L of water. The suspension is stirred at 35 °C for 30 minutes, cooled to 22-25°C and centrifuged again, washing finally with water (2 x 40 L). The water-moistened solid is suspended in 180 L of methanol and the mixture brought to reflux with stirring for 1 hour. The suspension fluidises but does not reach dissolution. It is cooled to 20-22 °C and the suspension

is stirred for 30 minutes. It is cooled to 0-5 °C and the suspension is stirred for 1 hour at that temperature. The suspension is centrifuged and the cake washed with 20 L of cold methanol. The product is dried at 60°C in vacuo for 15 hours. 10.8 kg of base ondansetron Form E (84%) is obtained.

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